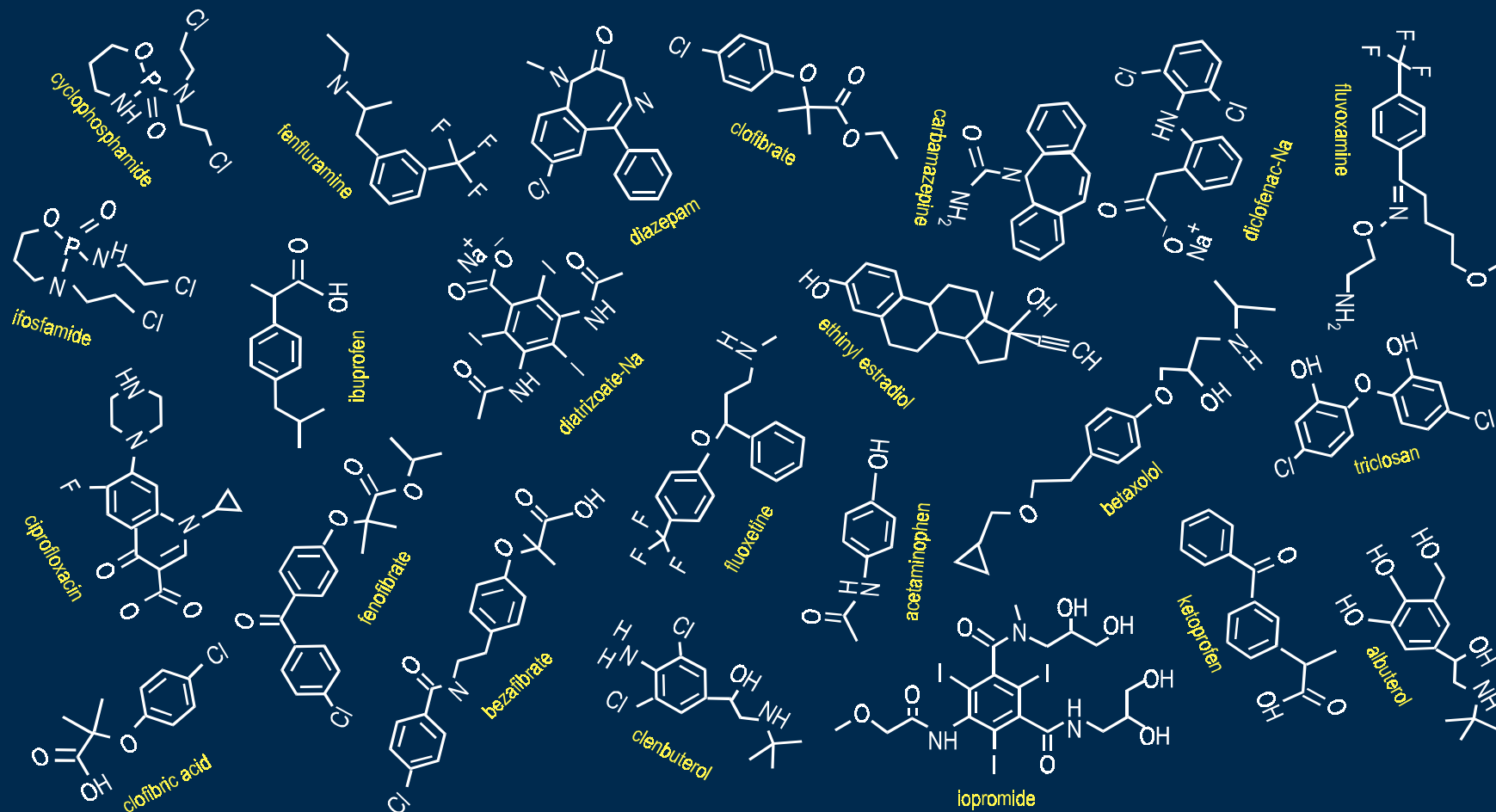


Pharmaceuticals and the Environment



Pharmaceuticals & Personal Care Products in the Environment

= Overview, Perspective & Focus <

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U.S. EPA Notice

The U.S. Environmental Protection Agency (EPA), through its Office of Research and Development (ORD), funded this research and approved the materials that formed the basis for this presentation. The actual presentation has not been peer reviewed by EPA.

**copy of this presentation
is available at:**

**[http://www.epa.gov/esd/
chemistry/pharma/index.htm](http://www.epa.gov/esd/chemistry/pharma/index.htm)**

The Materials on this Slide Show Result Largely from the Following Presentations

Daughton, C.G. “Pharmaceuticals in the Environment — Overarching Issues and Concerns,” paper #29, presented at the *219th National Meeting of the American Chemical Society*, session on Pharmaceuticals in the Environment, San Francisco, CA, 27 March 2000 (published in “Issues in the Analysis of Environmental Endocrine Disruptors”, Preprints of Extended Abstracts, vol 40(1), pp. 96-98, 2000).

Daughton, C.G. “Pharmaceuticals in the Environment — An Overview,” presented at the “Emerging Issues Conference,” sponsored by the National Ground Water Association, USGS Toxic Substances Hydrology Program, US EPA National Risk Management Laboratory, and Wessex Institute of Technology, UK; Minneapolis, MN, 7-8 June 2000.

Who might be interested in this topic?

- ▶ Those with a keen interest in the interconnectedness between humans and the environment.
- ▶ Some of the information presented here will hopefully lead to new insights, lend new perspectives, and enhance our knowledge of the linkage between humans and the environment.
- ▶ The materials presented here should prove of interest not just to those actively engaged in research, but also to educators, students, the public, and environmental risk assessors and policy makers.

Objectives of this Work

- ▶ Present an overview and background for the topic:
Environmental Aspects of Pharmaceuticals and Personal Care Products
- ▶ Highlight examples of current research from leading investigators in the field, covering some (but not all) aspects of the topic.
- ▶ Catalyze and promote further exploration and discussion of the issue by all stakeholders.
- ▶ Ensure that any regulatory decisions are based on sound science, avoiding being overly or under-protective of ecological or human health and wasting economic resources or jeopardizing health.

Limitations of Discussion

Any topic concerning potential environmental chemical pollution is multifaceted — involving a host of disciplines, including, in this case:

<Analytical/Environmental Chemistry <Toxicology <Hydrology <Medical Sciences <Sanitary Engineering <Risk Assessment <Policy Making

The materials presented here do not cover all the aspects of the overall topic, nor can they cover them in depth:

*<Chemical Analysis (methods for identification & quantitation)
<Identification of Source/Occurrence <Environmental Fate <Exposure
<Effects <Risk Assessment <Mitigation <Pollution Prevention
<Regulation <Research Planning & Coordination*

Clarification of Acronyms

Pharmaceuticals & Personal Care Products:
“PPCPs”

Endocrine Disrupting Compounds:
“EDCs”†

†a.k.a: environmental estrogens, endocrine-disruptors, endocrine-modulators, ecoestrogens, environmental hormones, xenoestrogens, hormone-related toxicants, hormonally active agents (HAAs), phytoestrogens (a naturally occurring subset).

“Disclaimers”

PPCPs vs. EDCs \cap PPCPs \cap EDCs

- ▶ PPCPs and EDCs are **not** synonymous — they are intersecting sets.
- ▶ Must avoid confusion regarding their relationship.
- ▶ Only a small subset of PPCPs are known/suspected of being **direct-acting** EDCs (e.g., synthetic steroids); toxicological concerns usually differ. EDCs comprise members from many disparate chemical classes.

continued -

“Disclaimers”

Origins of PPCPs in the environment:

End-Use vs. Manufacturing

- ▶ Focus of this discussion is primarily on PPCPs originating from **end-use** rather than from manufacturing.
- ▶ Emphasis is on use/disposal of PPCPs as originating primarily from activities/actions of individuals and to a lesser degree from hospitals and industry – not from the PPCP manufacturing sector (whose waste streams are much better defined, confined, and controlled/controllable).

continued -

“Disclaimers”

PPCPs as an “emerging” environmental issue?

While it is true that this issue has only recently become topical in the U.S., much research has already been accomplished over the last decade by a number of European and Scandinavian investigators.

- *concluded* -

CY 2000 Conferences on PPCPs

ACS (American Chemical Society) — *Pharmaceuticals and Personal Care Products in the Environment: An Emerging Concern*, 219th National Meeting of the American Chemical Society, San Francisco, CA, 27 March 2000.

[First all-day symposium in North America on this topic]

(<http://www.acs.org/meetings/sanfran2000/techprog.html>)

AWWARF (American Water Works Association Research Foundation) — *Endocrine Disruptors and Pharmaceutically Active Compounds in Drinking Water Workshop*, Chicago, Illinois, 19-21 April 2000 (<http://tango.cheec.uiowa.edu/awwarf/schedule.html>)

SETAC (Society of Environmental Toxicology and Chemistry), Third SETAC World Congress, 21-25 May 2000, Brighton, United Kingdom (<http://www.setac.org/eurpbrit.html>), Session 3C (and various others) “Veterinary and human pharmaceuticals - fate and effects”.

NGWA (National Groundwater Water Association) — *Emerging Issues Conference*, sponsored by the NGWA & USGS Toxic Substances Hydrology Program, US EPA National Risk Management Laboratory, and Wessex Institute of Technology, UK, Minneapolis, MN, 7-8 June 2000 (<http://www.ngwa.org/education/mnconf.html>)

SETAC (Society of Environmental Toxicology and Chemistry), *Environmental Science in the 21st Century: Paradigms, Opportunities, and Challenges*, proposed session: “Ecological Assessment – 3Z. Pharmaceuticals, Surfactants, & Other Contaminants in Aquatic Environments.” 21st Annual Meeting, Nashville Convention Center, 12-16 November 2000, Nashville, Tennessee (<http://www.setac.org/nashsess.html>)

CY 2001 Events: PPCPs

PLANNED BOOK: *American Chemical Society Symposium Series: “Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues”.*

Editors: C.G. Daughton & T. Jones-Lepp (U.S. EPA, ORD)

Publisher: American Chemical Society (distributed by: Oxford University Press)

Target Date: ca. early 2001; **ACS Contact:** Anne Wilson (Senior Product Manager, *ACS Symposium Series*; a_wilson@acs.org; 630-789-9683)

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SYMPOSIUM: “Pharmaceuticals in the Environment”,
(T.Ternes) *The 10th Symposium on Handling of Environmental and Biological Samples in Chromatography*, 1-4 April 2001,
Mainz/Wiesbaden, Germany (<http://www.dplanet.ch/users/iaeac>)

Research Funding Opportunities

EPA STAR: Research funding opportunity for the topic of *PPCPs in the Environment* is currently available through EPA/ORD's external grants program as described in the "2000 Environmental Research Grant Announcements" for "The Science to Achieve Results (STAR) Program"

available at: <http://es.epa.gov/ncerqa/rfa>

See the RFA for *Drinking Water*

available at: <http://es.epa.gov/ncerqa/rfa/drink00.html>

FY 2000 Science to Achieve Results (STAR) Program (National Center for Environmental Research)

Opening Date: April 17, 2000

Closing Date: July 31, 2000

[within the section on "Research on Health Effects of Chemical Contaminants," scroll down to the subsection on "Pharmaceuticals and personal care products."]

AWWARF: explore possibilities at: <http://www.awwarf.com>

Partial Basis and Background for Overview Presentation

- ▶ Daughton, C.G. and Ternes, T.A.
“Pharmaceuticals and personal care products in the environment: Agents of subtle change?” *Environmental Health Perspectives Supplement* 107(suppl 6):907-938 (December 1999).
- ▶ *Chemosphere* (issue devoted to drugs in the environment): volume 40, issue 7, pages 691-793 (April 2000).
- ▶ *Toxicology Letters* (special issue devoted to musks in the environment): volume 111, issue 1-2, pages 1-187 (Dec. 1999).
- ▶ Ternes T, Wilken R-D. (Eds.) Drugs and Hormones as Pollutants of the Aquatic Environment: Determination and Ecotoxicological Impacts. *The Science of the Total Environment* 225(1-2), 176 pp. (Jan. 1999).

Primary Goals of the U.S. EPA's *Office of Research and Development*

- ▶ **Identification of potential (future) environmental concerns:** forward thinking, planning, and research.
- ▶ **Proactive vs. Reactive — Pollution prevention vs. remediation/restoration:** Identify and foster investigation of “hidden” or potential environmental issues/concerns before they become critical ecological or human health problems.
- ▶ **Ruling-in/ruling-out vs. Uninformed rules:** Provide bases for informed decisions. Ensure that science leads eventual decisions for guidance or to regulate/not regulate.
- ▶ **Foster interdisciplinary research & collaboration:** Catalyze research by academe, private sector, government.

Drivers of Ecological Change

Ecological change is effected by human activities primarily via three routes:

- ▶ Habitat disruption/fragmentation.
- ▶ Alteration of community structure (e.g., introduction alien/nuisance species).
- ▶ Chemical pollution.

The scopes/ramifications of first two are highly delineated compared with chemical pollution.

“PBTs” and “POPs” – only one part of the risk puzzle?

During last three decades, the impact of chemical pollution has focused almost exclusively on conventional “priority pollutants”[†], especially on those collectively referred to as “persistent, bioaccumulative, and toxic” (PBT) pollutants or “persistent organic pollutants” (POPs).

The “dirty dozen” is a ubiquitous, notorious subset of these, comprising highly halogenated organics (e.g., DDT, PCBs).

The conventional priority pollutants, however, are only one piece of the larger risk puzzle.

[†] it is important to recognize that the current “lists” of priority pollutants were primarily established in the 1970's in large part for expediency — that is, they could be measured with off-the-shelf chemical analysis technology. Priority pollutants were NOT necessarily selected solely on the basis of risk.

“Emerging” Risks

Previously unidentified or under-appreciated aspects of chemical pollution often involve chemical classes not before recognized as pollutants — there is nothing rigorous or definitive about the established lists of pollutants.

However, any concern for ecological or human health risk posed by newly considered chemical classes must have a scientific basis in environmental **occurrence**, **exposure**, and ultimately a measurable **effect**.

One of the EPA’s 10 Strategic Plan goals — Goal 8 (*Sound Science*): Improved Understanding of Environmental Risk, and Greater Innovation to Address Environmental Problems [see: <http://www.epa.gov/ocfopage/plan/plan.htm>]

continued -

“Emerging” Risks

It is reasonable to surmise that the occurrence of PPCPs in waters is not a new phenomenon. It has only become more widely evident in the last decade because continually improving chemical analysis methodologies have lowered the limits of detection for a wide array of xenobiotics in environmental matrices. There is no reason to believe that PPCPs have not existed in the environment for as long as they have been used commercially.

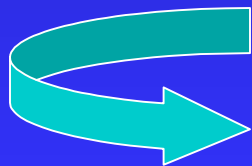
- concluded -

Pharmaceuticals and Personal Care Products (PPCPs)

Fact: Certain PPCPs occur in the environment (esp. the aquatic environment)

Origins: Domestic sewage, hospitals, CAFOs

Issue: Fate and effects are poorly understood



Numerous questions...

PPCPs as Environmental Pollutants?

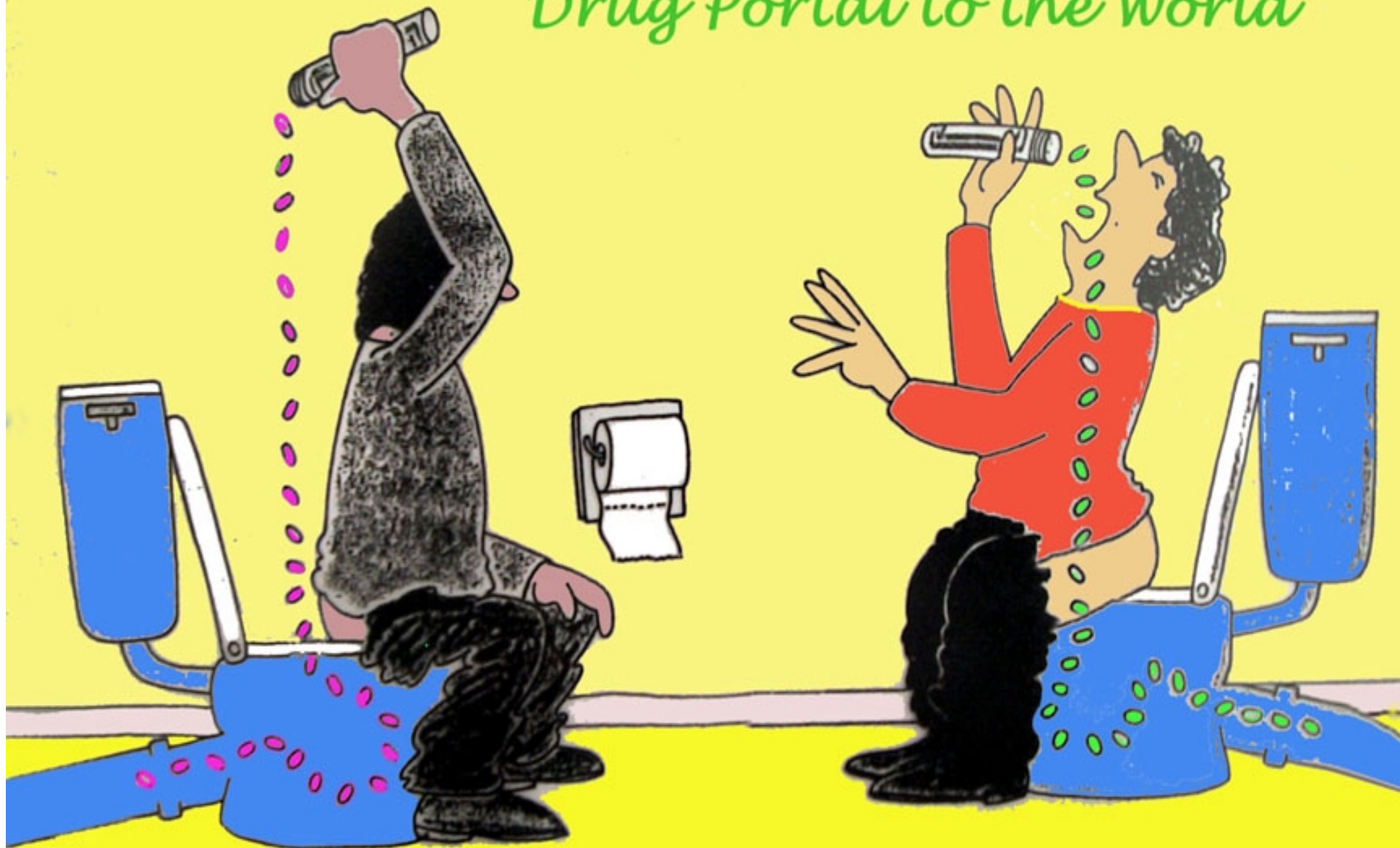
- ▶ PPCPs are a diverse group of chemicals comprising all **drugs** (available by prescription or over-the-counter; including the new genre of “biologics”), **diagnostic agents** (e.g., X-ray contrast media), “**nutraceuticals**” (bioactive food supplements such as huperzine A), and other consumer chemicals, such as **fragrances** (e.g., musks) and **sun-screen agents** (e.g., methylbenzylidene camphor).
- ▶ Drugs differ from agrochemicals in that they often have multiple functional groups (many are amphiphilic) and usually have lower effective doses. This complicates fate/transport modeling and lends an extra dimension to the analytical techniques required for monitoring. Also designed for use by/for the individual.
- ▶ In contrast to the conventional PBTs, most PPCPs are neither bioaccumulative nor volatile; some, such as the musks, however, do indeed fulfill the criteria for PBTs.

Origins of PPCPs in the Environment

- ▶ Portions of most ingested drugs are excreted in varying unmetabolized amounts (and undissolved states, primarily because of protection by excipients) primarily via the feces and urine.
- ▶ Other portions sometimes yield metabolites that are still bioactive. Still other portions are excreted as conjugates.
- ▶ Free excreted drugs and derivatives can escape degradation in municipal sewage treatment facilities (removal efficiency is a function of the drug's structure and treatment technology employed); the conjugates can be hydrolyzed back to the free parent drug.
- ▶ Un-degraded molecules are then discharged to receiving surface waters or find their way to ground waters, e.g., leaching, recharge.

continued -

Drug Portal to the World



adapted by Daughton from Ternes (April 2000)

Origins of PPCPs in the Environment

- ▶ Other potential routes to the environment include leaching from municipal landfills, runoff from confined animal feeding operations (CAFOs) and medicated pet excreta, loss from aquaculture, spray-drift from agriculture, direct discharge of raw sewage (storm overflow events & residential “straight piping”), and transgenic production of proteinaceous therapeutics by genetically altered plants (aka “molecular farming” — “biopharming”).
- ▶ Direct discharge to the environment also occurs via dislodgement/washing of externally applied PPCPs.

- concluded -

Questions Deserving Attention?

- ▶ “Conventional”, regulated lists of “priority pollutants” (e.g., POPs) — Are POPs the only chemicals that deserve our attention regarding environmental fate and effects?
- ▶ PPCPs in aquatic environments receiving treated & untreated sewage (overflows/spills & “straight-piping”) — What is the spectrum of PPCP occurrence and prevalence?
- ▶ PPCPs leaching into groundwater from solid waste disposal or sewage sludge application — Is there any significance to PPCPs in groundwater? Are they persistent?
- ▶ PPCPs in treated wastewater intended for groundwater recharge — Is there cause for concern from recycled water?

continued -

Questions Deserving Attention?

- ▶ Low concentrations of PPCPs in the environment (especially in the aquatic realm) — Is there cause for concern regarding impact to non-target organisms?
- ▶ Potential effects of PPCPs on non-target species, many of which do not possess the same suite of receptors as humans — Do we know enough about receptor differences and similarities among target and non-target organisms?
- ▶ Individual PPCPs at low concentrations — Can multiple PPCPs sharing the same mode of action combine to reach threshold-effects levels?

continued -

Questions Deserving Attention?

- ▶ PPCPs that are continually introduced to aquatic environment — Is this a special exposure case since biota are exposed continually, through multiple generations?
 - ▶ Cellular mechanisms in aquatic biota that confer protection from continual exposure (e.g., efflux pumps) — Can these protective cellular transport systems be inhibited by certain PPCPs, thereby compromising aquatic health?
 - ▶ Acute toxicity, carcinogenesis, and mammalian endocrine disruption are highly visible concerns for many environmental pollutants — Should more attention be paid to other, less overt toxicological endpoints, such as immuno-disruption, neurobehavioral change, and other subtle effects?
- continued -*

Questions Deserving Attention?

- ▶ Practices partly contributing to introduction of PPCPs to the environment include direct disposal of excess/expired PPCPs to domestic sewage and landfills, and over-prescribing of various drugs — Should these practices be discouraged?
- ▶ Low levels of PPCPs in drinking water and shell/fin-fish — Can consumption by humans lead to significant exposures?
- ▶ In short: Is there the potential for unanticipated consequences of PPCPs in the environment? If so, where's the evidence? Do sufficient data exist to decide whether certain classes of PPCPs in the environment warrant a careful look, or can we ignore other classes?

- *concluded* -

Overview: Pharmaceuticals in the Environment

- ▶ Certain pharmaceutically active compounds (e.g., caffeine, aspirin, nicotine) have been known for over 20 years to occur in the environment.
- ▶ Environmental occurrence primarily resulting from treated and untreated sewage effluent.
- ▶ Only more recently has a larger picture emerged — numerous PPCPs can occur (albeit at very low concentrations).
- ▶ Domestic sewage is a major source — not just hospital sewage.

continued -

Overview: Pharmaceuticals in the Environment

- ▶ Continual input of PPCPs to aquatic environment via sewage can impart a persistent quality to those compounds that otherwise possess no inherent environmental stability.
- ▶ The full extent, magnitude, and ramifications of their presence in the aquatic environment are largely unknown.
- ▶ Vast majority of all ecological monitoring studies to date have been performed in Europe.
- ▶ Use/release of antibiotics and natural/synthetic steroids to the environment has generated most of the controversy to date, but a plethora of other PPCPs have yet to be examined. Scope of overall issue is ill-defined.

continued -

Overview: Pharmaceuticals in the Environment

- ▶ Toxicological significance for non-target organisms (esp. aquatic) is poorly understood.
- ▶ If PPCPs eventually prove to be an environmental concern, it is unknown whether sewage treatment facilities could be cost-effectively modified to reduce emissions.
- ▶ Focus should be on proper and sufficient science for establishing occurrence, exposure, susceptibility/effects, so that sound decisions can be made regarding human and ecological health; note that establishment of “occurrence” of a PPCP includes not just its structural identification, but also its concentration, frequency, and geographic extent and distribution for a given environmental matrix.

- *concluded* -

Major Tasks for Science Community

- ▶ Determine which therapeutic or consumer-use classes of PPCPs have an environmental presence.
- ▶ For each PPCP class known to be present in the environment at significant individual or combined concentrations, rule-in or rule-out possible deleterious environmental effects.
- ▶ Task will involve simultaneous work from both exposure and effects scientists working in parallel and in sequence.

Inter-Connectedness of Humans and the Environment

- ▶ Occurrence of PPCPs in the environment mirrors the intimate, inseparable, and immediate connection between the actions and activities of individuals and their environment.
- ▶ PPCPs owe their origins in the environment to their worldwide, universal, frequent, and highly dispersed but cumulative usage by multitudes of individuals.

Aquatic organisms — captive to continual, life-cycle chemical exposures

- ▶ **Aquatic Exposure is Key:** Any chemical introduced via sewage to the aquatic realm can lead to continual, multigenerational exposure for aquatic organisms.
- ▶ **Re-evaluation of “persistence”:** Chemicals continually infused to the aquatic environment essentially become “persistent” pollutants even if their half-lives are short — their supply is continually replenished (analogous to a bacterial chemostat).

Subtle (currently unrecognized) Effects: a Troubling Scenario?

- ▶ Uses for which PPCPs were designed differ radically from those of industrial and agro-chemicals.
 - ▶ Intended biological targets (receptors) are numerous and frequently exquisitely specific and sensitive.
 - ▶ Intended/unintended receptors of exposure and effects can differ greatly from those of currently regulated pollutants.
 - ▶ Receptors in non-target species could differ from those in humans.
- continued -*

Subtle (currently unrecognized) Effects:

some examples:

- ▶ Profound effects on spawning and other behaviors in shellfish by antidepressant **SSRIs**.
- ▶ Dramatic inhibition of sperm activity in certain aquatic organisms by **calcium-channel blockers**.
- ▶ **Antiepileptic** drugs (e.g., phenytoin, valproate, carbamazepine) have potential as human neuroteratogens, triggering extensive apoptosis in the developing brain → neurodegeneration.
- ▶ Multi-drug transporters (efflux pumps) are common defensive strategies for aquatic biota — possible significance of **efflux pump inhibitors** in compromising aquatic health?

continued -

Subtle Effects: Multi-Drug Transporters

- ▶ General “Chemical Defense System” in aquatic biota
- ▶ Multi-drug transporters — a.k.a. efflux pumps — confer “multi-drug resistance” (MDR) or multi-xenobiotic resistance (MXR).
- ▶ Membrane-based active transport systems that “eject” or “pump” toxicants from inside cells (best characterized are the “P-glycoprotein-like” – Pgp – transporter systems).
- ▶ Prevent intracellular accumulation of toxicants and bioactive metabolites — allow cellular functioning in presence of extracellular toxicant concentrations that would otherwise prove toxic.

continued -

Subtle Effects: Multi-Drug Transporters

- ▶ Any of a diverse array of certain chemicals can inhibit these pumping systems, thereby potentiating adverse effects from extracellular toxicant concentrations that otherwise prove benign.
- ▶ Efflux Pump Inhibitors: a.k.a. “efflux pump reversal agents”, “chemosensitizers”, “efflux pump blockers”, or “efflux pump inhibitors” (EPIs) [some of more potent being verapamil, reserpine, cyclosporin].
- ▶ Now recognized for enabling significant portion of increasing incidence of antimicrobial resistance among bacteria, these systems may also play critical role in protecting cells from toxicants (e.g., esp. in aquatic realm where filter-feeding organisms suffer continual, maximal exposure to toxicants).

continued -

Subtle Effects: Multi-Drug Transporters

- ▶ When aquatic MXR is expressed, intracellular concentration of toxicants will not accurately reflect actual exposure concentrations. When body-burdens of pollutants in aquatic organisms are used as indicators for exposure concentrations, the lower-than-expected bioaccumulated loads will bias these extrapolations low.
- ▶ Does the continual need to express and maintain high-levels of MXR impose a burdensome energy cost on aquatic organisms, thereby jeopardizing overall health or survival advantage?
- ▶ Would organisms in less-polluted aquatic environments be at higher risk to newly introduced toxicants because of their lower induced levels of MXR?
- ▶ Can broad-spectrum antiseptics such as triclosan promote widespread antibiotic resistance simply by inducing efflux pumps?

continued -

Subtle Effects: Multi-Drug Transporters

- ▶ Those chemicals that induce expression of efflux pump systems add another dimension to potential impacts by selectively enriching populations for resistant individuals (of seemingly good health) but paradoxically placing the entire population at maximum risk should they eventually be exposed to potent EPIs.
- ▶ Can systems in apparent good health possibly collapse simply by exposure to one or a series of EPIs (which by themselves would not prove toxic), simply from potentiating the action of toxicants that were already present?
- ▶ **Summary of MXR:** Cellular expression of these transport systems serves simultaneously as a marker of exposure, as a marker of effects, and as an indication of overall “health” (i.e., the ability to survive adverse chemical exposures). *continued -*

Subtle (currently unrecognized) Effects: a Troubling Scenario?

- ▶ Could immediate biological actions on non-target species be imperceptible but nonetheless lead to adverse impacts as a result of continual accretion over long periods of time?
- ▶ Could subtle effects accumulate so slowly (perhaps seeming to be part of natural variation) that major outward change cannot be ascribed to the original cause?
- ▶ Effects that are sufficiently subtle that they are undetectable or unnoticed present a challenge to risk assessment (especially ecological).
- ▶ Advances required in developing/implementing new aquatic toxicity tests to better ensure that such effects can be detected.

- *concluded* -

Example BOTE Calculation for SSRIs in Sewage from a Major Municipal System

Facts:

Fluvoxamine elicits mussel spawning at 318 ng/L (see refs by Fong as cited by Daughton & Ternes 1999).

Example county population >1.25 million.

140 Mgal (530 ML) sewage processed per day.

Fluvoxamine, fluoxetine, and paroxetine are administered roughly in the 20-300 mg/day range.

Assumptions (simplistic, but realistic):

Average dosage regime of 50 mg/day for each of these three SSRIs (there are other SSRIs) (conservative assumption).

Only 2% of unaltered parent compound is excreted and SSRs (metabolites -- there are many) harbor 1/20th of the parent drugs' activities (realistic assumption).

One-tenth of population takes one of these three drugs (reasonable assumption).

No metabolism of SSRIs in STW (overly conservative assumption).

Total daily amount of SSRIs potentially introduced to an example county's receiving waters per day:

$1.25 \times 10^6 \text{ people} \times 10^{-1} \times 50 \text{ mg/day-person} \times (0.02 \text{ mg active ingredient/mg parent ingredient} + 0.98/20 \text{ active metabolite/mg parent ingredient}) =$

$1.25 \times 10^5 \times 3.5 \text{ mg/day} =$

$4.4 \times 10^5 \text{ mg/day} \Rightarrow 4.4 \times 10^5 \text{ mg/day} \times 530^{-1} \text{ day/ML} = 8.3 \times 10^2 \text{ mg/ML} \times 10^{-6} \text{ ML/L} = 8.3 \times 10^{-4} \text{ mg/L} =$

$\Rightarrow 0.83 \text{ } \mu\text{g/L}$ (ca. 1 ppb) in treated effluent

This exceeds the amount of fluvoxamine required for effects in mussels, but is probably less than the amount required for the other SSRIs. Combined effects from other SSRIs have not been considered here. This is only one of many effects that have been noted for shellfish (which, while not relevant to some aquatic locales, is merely meant to be illustrative for sewage discharges).

Unintended, Unexpected Effects

- ▶ Adverse (idiosyncratic) drug reactions in humans can be caused by previously unrecognized drug-receptor interactions, previously unidentified receptors, and by a broad diversity in drug-metabolizing/transport phenotypes (genetic polymorphisms).
- ▶ These variables are even more poorly characterized in aquatic biota.
- ▶ Just as animal models are frequently called into question for their relevance to human health, likewise, human and other mammalian toxicity data (e.g., from PPCPs) are not necessarily transferable to aquatic organisms.
- ▶ The use of certain drugs during critical times of development for fetuses, infants, and children is severely restricted because of the potential for serious adverse effects — timing of exposure with developmental stage is critical. These same drugs, however, if delivered to the aquatic environment, would enjoy no restrictions to prevent the exposure of developing non-target organisms.

Toxicological Endpoints – The need to expand the horizon?

- ▶ Up to recently, the historical primary endpoints of interest in risk assessment have been acute toxicity and carcinogenesis — little attention has been paid to the universe of other endpoints through which toxicants can exert their action.
- ▶ Other endpoints, such as neurobehavioral, immunological, and endocrine homeostasis alterations, can be very subtle but nonetheless lead to unanticipated, profound outcomes.
- ▶ Subtle endpoints could also be effected by extremely low concentrations of a toxicant (difficult to empirically test).
- ▶ Effects mediated (e.g., via hormone-like compounds) do not necessarily follow the monotonic sigmoid dose-response curve (U- and inverted-U-shaped curves can occur). *continued-*

Toxicological Endpoints (cont'd)

- ▶ Effects on non-target organisms could differ between (and within) each class of PPCPs – the receptors being different for antimicrobials, endocrine modulators, SSRIs, antineoplastics, etc.
- ▶ This fact, coupled with a large spectrum of species (both aquatic and terrestrial) that could experience exposure, means that a very large array of toxicity screening procedures could be needed — prospects for a single apical assay are low.
- ▶ Accounting for wild-type drug-metabolism/transport polymorphisms further complicates any screening approach.

continued -

Toxicological Endpoints (cont'd)

- ▶ The priorities for selecting PPCPs for toxicological evaluation can NOT be based on their relative rankings of environmental concentrations simply because drugs can dramatically vary with respect to the concentrations at which they impart effects — sometimes by orders of magnitude.
- ▶ Response thresholds can be much lower for real-world chronic exposure (e.g., free, wild fish) than for short-term study exposures (e.g., for caged fish). Responses can be a function of not just the dose, and timing of dose, but also duration of exposure. Response thresholds (no-effect concentrations) can be continually reduced as exposure times increase.

- *concluded* -

Classes of PPCPs Identified in Environmental Samples

- ▶ In addition to antimicrobials and steroids, over 50 individual PPCPs or metabolites (from more than 10 broad classes of therapeutic agents or personal care products) have been identified (up to 1999) in environmental samples (mainly in sewage, surface, and ground waters).
- ▶ It is important to note, however, that although a number of representatives from this subset of therapeutic classes have been identified in the environment, members of most classes have yet to be searched for.

continued -

PPCP Classes Identified in Environmental Samples

Representative classes (and members) of PPCPs reported in environmental samples.

therapeutic class	example Brand name	generic name
analgesics/ non-steroidal anti- inflammatories (NSAIDs)	Tylenol Voltaren Advil Oruvail Naprosyn	acetaminophen diclofenac ibuprofen ketoprofen naproxen
antimicrobials	many	e.g., sulfonamides, fluoroquinolones
antiepileptics	Tegretal	carbamazepine
antihypertensives (betablockers, beta- adrenergic receptor inhibitors)	Concor Lopressor	bisoprolol metoprolol
antineoplastics	Cycloblastin Holoxan	cyclophosphamide ifosfamide
antiseptics	Igrasan DP 300	triclosan
contraceptives	Oradiol	17 α -estradiol 17 α -ethinyl estradiol
β 2-sympathomimetics (bronchodilators)	Ventolin	albuterol
lipid regulators (anti- lipidemics; cholesterol- reducing agents; and their bioactive metabolites)	Atromid-S Lopoid	clofibrate (clofibric acid metabolite) gemfibrozil
musks (synthetic)	musk xylene Celestolide substituted amino nitrobenzenes	nitromusks polycyclic musks reduced metabolites of nitromusks
anti-anxiety/hypnotic agents	Valium	diazepam
sun screen agents	Eusolex 6300	methybenzylidene camphor
X-ray contrast agents	Hypaque	diatrizoate

Majority of PPCP classes have no environmental survey data

- ▶ Environmental survey data have yet to be reported for many classes (and class members) of PPCPs.
- ▶ While the literature is silent regarding these PPCPs, is this because of an absence of data or a failure to report “data of absence”?
- ▶ Many of these unreported drugs are among the most widely prescribed in the U.S.

continued -

PPCPs with no environmental survey data

Representative distinct classes of drugs for which concerted environmental surveys have not been performed

(bolded names among top 200 most prescribed in U.S.: <http://www.rxlist.com/top200a.htm>)

therapeutic class	example generic names (many drugs cross over into multiple classes)	example Brand names
adrenergic receptor inhibitors (anti-BPH agents)	terazosin , doxazosin , finasteride	Hytrin, Cardura, Proscar/Propecia
amyotrophic lateral sclerosis	riluzole	Rilutek
analgesics (non-NSAIDs and narcotic)	tramadol , propoxyphene , oxycodone , hydrocodone	Darvon, Ultram, Tylox
anorexiant (diet drugs)	fenfluramine, orlistat	Pondimin, Xenical
antiarrhythmics	disopyramide, flecainide, amiodarone, sotalol	Norpace
anticoagulants	warfarin	Coumadin
antidepressants	esp. SSRIs (sertraline , paroxetine , fluoxetine , fluvoxamine), tricyclics (desipramine), MAOIs (phenelzine), misc.	Zoloft, Paxil, Prozac, Luvox, Wellbutrin (bupropion), Serzone (nefazadone), Effexor (venlafaxine)
antidiabetic agents	insulin sensitizers, antihyperglycemic (e.g., sulfonylureas)	Rezulin (troglitazone), Glucophage (metformin), Glucotrol (glipizide), DiaBeta (glyburide)
antihistamines (H-1 blockers)	fexofenadine , loratadine , cetirizine , terfenadine	Allegra, Claritin, Zyrtec, Seldane
histamine (H-2) blockers	famotidine , ranitidine ,	Pepcid, Zantac, Axid

PPCPs with no environmental survey data

cont'd: Classes of Drugs Lacking Concerted Environmental Surveys

histamine (H-2) blockers	famotidine, ranitidine, nizatidine	Pepcid, Zantac, Axid
decongestants	ephedrine	
anti-infectives	many special disease classes (amebicides, anti-fungals, malarials, tuberculosis, leprosy, viral) & chemical classes	Diflucan (fluconazole)
antimetabolites	methotrexate	Rheumatrex
antipsychotics, CNS agents	alprazolam, zolpidem, clonazepam, risperidone, temazepam thioridazine, rifluoperazine	Xanax, Ambien, Klonopin, Risperdal, Restoril
calcium-channel blockers	diltiazem, nifedipine, amlodipine, verapamil	Cardizem, Procardia, Norvasc
digitalis analogs	digoxin , digitoxin	Lanoxin
diuretics	thiazide (hydrochlorothiazide , chlorthalidone); loop (furosemide, bumetanide); potassium-sparing (spironolactone, triamterene)	Lasix (furosemide) Dyazide (hydrochlorothiazide, triamterene)
dopamine agonists	anti-Parkinsonian agents (e.g., pramipexole, ropinirole)	Mirapex, Requip
expectorants	guaifenesin	Entex
gastrointestinal agents	omeprazole	Prilosec, Prevacid

PPCPs with no environmental survey data

cont'd: Classes of Drugs Lacking Concerted Environmental Surveys

dopamine agonists	anti-Parkinsonian agents (e.g., pramipexole, ropinirole)	Mirapex, Requip
expectorants	guaifenesin	Entex
gastrointestinal agents (ulcer drugs)	omeprazole, lansoprazole, cimetidine	Prilosec, Prevacid, Tagamet
HIV drugs	protease inhibitors, anti- retrovirals (nucleoside analog reverse transcriptase inhibitors)	Crixivan (indinavir), Retrovir (zidovudine)
hormonally active agents androgens anti-acne agents adrenocortico- steroids inhalable steroids estrogen antagonists	flouxymesterone isotretinoin, tretinoin prednisone, triamcinolone fluticasone tamoxifen	Accutane, Retin-A Flovent Nolvadex
muscle relaxants	cyclobenzaprine	Flexeril
osteoporosis agents	alendronate sodium	Fosamax
prostaglandin agonists	latanoprost	Xalatan
psychostimulants (amphetamine-like)	methylphenidate, dextroamphetamine	Ritalin
sexual function agents	sildenafil citrate	Viagra
street drugs (illicit, illegal, recreational)	many: e.g., see listing at: "Streetdrug.org" (http://www.mninter.net/%7epublish/index2.htm)	

PPCPs with no environmental survey data

concluded: Classes of Drugs Lacking Concerted Environmental Surveys

psychostimulants (amphetamine-like)	methylphenidate, dextroamphetamine	Ritalin
sexual function agents	sildenafil citrate	Viagra
street drugs (illicit, illegal, recreational)	many: e.g., see listing at: "Streetdrug.org" (http://www.mninter.net/%7epublish/index2.htm)	
vasodilators (esp. angiotensin converting enzyme [ACE] inhibitors)	lisinopril, enalapril, quinapril, benazepril losartan, fosinopril, ramipril	Zestril, Vasotec, Accupril, Lotensin Cozaar, Monopril
newly approved, upcoming, and investigational drugs	Ongoing: see listing at: "Lexi-Comp.org" (http://www.lexi.com/new_drugs.htm)	
"chemosensitizers", efflux pump inhibitors (EPIs)	verapamil (and others from diverse classes; e.g., http://www.microcide.com/ICAAC99 Posters/icaac99_posters.html)	

The Future for Research on PPCPs in the Environment

- ▶ Poorly characterized ramifications of PPCPs in the environment (occurrence, fate, transport, effects) warrant a more precautionary view on their environmental disposition.
- ▶ A portion of the effort that continues to be invested in elucidating the environmental transformation and fate of POPs/PBTs might be better redirected to PPCPs.
- ▶ One area that should be pursued immediately is a search of the literature for unintended, unexpected effects, especially related to aquatic organisms, with some emphasis on efflux pump inhibitors/promoters.

Near-term actions to minimize introduction of drugs to environment or their potential effects

- ▶ **Screening for EPI Potential:** Develop new aquatic testing procedures (esp. cellular based); evaluate possible impacts of potent, new-generation efflux pump inhibitors (EPIs).
- ▶ **Environmental “Friendliness”:** Factor environmental proclivity into PPCP design/marketing “green” PPCPs: maximize biodegradability/photolability to innocuous end products, minimize therapeutic dose (“calibrated dosing”), single-enantiomers.
- ▶ **Drug Prescribing & Use:** Better inform physicians (and public) to environmental consequences of over-prescribing medications — minimize misuse/overuse. Engage medical community to develop guidelines. Identify pathogens prior to prescribing antibiotics (“imprudent use”). *continued -*

Near-term actions (cont'd)

► **Internet Dispensing:** Educate/encourage the pharmacy community to understand environmental consequences of over-dispensing (and dispensing without a prescription) to minimize unneeded drug use and attendant disposal [see: www.fda.gov/oc/buyonline].

► **Individualization of Therapy:** Encourage drug manufacturers to provide medical community with the necessary information to tailor drug dosages to the individual (esp. long-term maintenance drugs) on basis of body weight, age, sex, health status, and known individual drug sensitivities — individualization of therapy. Identify lowest effective dosages (“calibrated dosing”).

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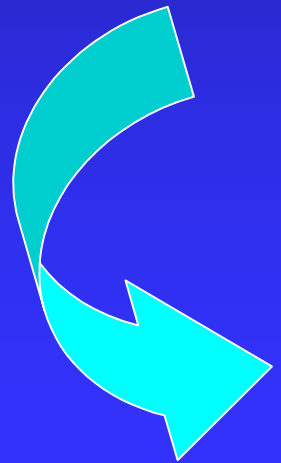
Near-term objectives (cont'd)

- ▶ **Proper Disposal:** Better inform pharmacy industry to provide proper disposal instructions to end-user for unused/expired drugs. Better guidance for disposition of non-controlled substances by disposal companies. Consider implementing Extended Producer Responsibility (EPR).
- ▶ **Importance of Individuals' Actions:** Educate public on (i) how their individual actions each contributes to burden of PPCPs in the environment, (ii) how PPCPs can possibly affect aquatic biota, and (iii) the advantages accrued by conscientious/responsible disposal and usage of PPCPs.
- ▶ **Use of Drugs as Environmental Markers of Sewage:** Capitalize on occurrence of certain, more easily degraded PPCPs to serve as conservative markers/tracers of discharge (early warning) of raw (or insufficiently treated) sewage.

- *concluded* -

Summary Distillation of the Significance of PPCPs in the Environment

Using the “risk assessment paradigm” as an organizing framework, we can consider the factors of pollutant source, occurrence/exposure, effects, and pollution prevention, and encapsulate the overall issue of PPCPs in the environment as follows:



Summary — 1 — PPCP Sources

All chemicals applied externally or ingested (and their bioactive transformation products) have potential to be excreted/washed into sewage systems and from there discharged to the aquatic/terrestrial environments.

Input to the environment is a function of the efficiency of human absorption/metabolism and the efficiency of the treatment technologies employed (if any). Efficiencies vary from chemical to chemical and between sewage treatment facilities. Obviously, discharge of untreated sewage maximizes occurrence of PPCPs in the environment.

- ▶ **Non-Point Sources:** Importance of dispersed, diffuse, non-point “discharges” of anthropogenic chemicals to environment has been overshadowed for decades by the more obvious point sources.
- ▶ **Importance of Individual Action:** Importance and significance of individuals in directly contributing to the combined load of chemicals in environment has been largely overlooked.
- ▶ **“Connectedness”:** PPCPs illustrate immediate, intimate, & inseparable connection of the actions/activities of the individual with environment.

continued -

Summary — 2 — Occurrence/Exposure

An extraordinarily limited subset of tens of thousands of commerce/industrial chemicals has been the narrow focus of environmental chemists for decades.

- ▶ **The Larger Puzzle:** Consideration of PPCPs as an additional class of long-ignored chemicals in exposure would contribute to the larger risk assessment puzzle and lend more perspective in the quest for “holistic” risk assessments.
- ▶ **Toxicity Out of Context:** Environmental toxicologists are usually forced to look at exposure issues “out of context” because of the extreme complexity of factoring in exposure from all potential toxicants that may be present in any given exposure situation (and the lack of comprehensive chemical analysis data).
- ▶ **Limited View of Persistence:** Our view of pollutant “persistence” might not be sufficiently encompassing being that the continual introduction of PPCPs to the aquatic environment via sewage outfalls could potentially lead to continual exposure even though a pollutant may not be truly “persistent”.
- ▶ **Aquatic Exposure the Major Concern:** Exposure risks for aquatic organisms are much larger than those for humans, given much lower potential concentrations in upgraded (treated) domestic drinking water and the fact that aquatic organisms suffer continual, multi-generational exposures to any chemical in their domain.

continued -

Summary — 3 — Effects

Drugs are purposefully designed to interact with cellular receptors at low concentrations and to elicit specific biological effects. Unintended adverse effects can also occur from interaction with non-target receptors.

- ▶ **Traditional Toxicology:** Environmental toxicology has long focused on the more obvious, acute effects of exposure.
- ▶ **Shift of Focus to Subtle Effects:** Any concern with PPCPs in the environment (and if/when present, they would be expected to be at very low concentrations) points to the need for development of tests that detect more subtle end-points (neurobehavioral effects and inhibition of efflux pumps being two examples).
- ▶ **Little data:** While sparse aquatic/terrestrial toxicology data exists for PPCPs, the little that has been published shows the potential for subtle effects (that could escape our immediate attention) at low concentrations.
- ▶ **Antibiotics:** Of course, more obvious consequences are actively being debated, such as the promotion of antibiotic resistance in pathogens from the (over?)use of antimicrobials in people, animals, and agriculture.

continued -

Summary — 4 — Pollution Prevention

Pollution prevention is preferable to remediation

Proactive vs. Reactive approaches

- ▶ **Central Importance of the Individual:** In closing the loop (from pollution prevention back to source), the most overlooked key to minimizing environmental pollution is the importance of the individual — including the user/consumer and the prescribing/dispensing professional communities.
- ▶ **Actions to Consider:** A variety of actions can be considered by all involved (including manufacturers) to minimize society's use of PPCPs while still accruing full benefit from these largely useful, beneficial, and often extremely important chemicals. Importance of "Extended Product Responsibility".

- *concluded* -

“Take-Home” Message

PPCPs in the environment mirror its direct connection with human activities and actions

- ▶ By reducing the consumption and disposal of PPCPs, benefits could accrue to both humans and to the environment.
- ▶ The reduction in use of types and quantities (e.g., dosages) of antibiotics and other drugs could reduce side effects and lessen the likelihood of pathogen resistance development.
- ▶ “Calibrated dosing” and more enlightened disposal methods would lessen the burden of PPCPs on the environment.

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So What ?!?

In the absence of definitive environmental or human health effects data resulting from actual exposure to environmental levels (which, after all, are far below therapeutic dosages) why should we be concerned ?

While drugs might occur in domestic potable waters at extremely low concentrations, we must be wary of dismissing the toxicological significance for humans (or aquatic life) of low concentrations (ppt) of drugs in drinking water on the sole basis that such concentrations are orders of magnitude lower than the therapeutic dosages (amounting to merely nanograms-per-day intakes via drinking water). This remains a common assertion in prognostications of potential minimal human health effects (or absence of) and is potentially flawed for any number of the following reasons...

- continued -

... because ...

In addition to advantages of being proactive versus reactive, several variables are not considered by this question...

- ▶ epidemiological studies ascribing effects to common pollutants (e.g., PBTs) do not factor in exposure to other, unconventional pollutants (because they are not measured or considered in these studies),
- ▶ recommended therapeutic dosages can be higher than the therapeutic dose actually required (a result of not individualizing therapy),
- ▶ non-target, unintended effects can not be discounted at sub-therapeutic dosages (unintended effects can often occur at lower concentrations than do therapeutic effects, especially during maintenance therapy),
- ▶ additive/synergistic effects from simultaneous consumption of numerous drugs are essentially unknown (added complexity of additional burden to patient already taking a medication having a low therapeutic index), and
- ▶ continual, life-long exposure to trace levels — an unexplored domain of toxicology.

- *concluded*

A Postscript

The Fragmentation of Science - Loss of the Bigger Picture **Critical Importance of *Knowledge “Mining”* and *Synthesis***

Much of the world's published science literature is vastly underutilized and highly fragmented. With respect to environmental aspects of PPCPs, the medical literature in particular has yet to be effectively utilized to address ecological effects questions.

While the information available in any research field continues to grow exponentially, proportionately less time is devoted in trying to “mine” and capture this knowledge to synthesize a larger picture.

Literature is often ignored or simply becomes “lost” to future investigators. The paradoxical message is that the published literature is not as important as “new” findings.

Duplication of effort and reinvention of the wheel are symptoms of the failure to pay sufficient attention to the literature.

A parallel problem is that the larger picture remains obscure when the literature is not critically examined, especially for issues that cross multiple disciplines.

Solutions to problems and answers to questions can be waiting to be “discovered” amidst research that has already been reported.

continued -

Postscript (concluded)

This problem relates in part to the fact that there is little professional reward in attempting to distill, synthesize, and integrate what is known about a topic. Science managers tend to value publication of "original" data — even if it is incremental, and even, unbeknownst to them, if it is merely "rediscovered" data.

Furthermore, scientists often do not understand the significance, impact, or relevance of their work because they are caught in the drive to publish — at the expense of reading, comprehending, distilling, synthesizing, and communicating.

The issue of "capture and synthesis" of fragmented knowledge has been discussed by Prof. Peter Csermely (Semmelweis University, Budapest) in "Limits of Science Growth" (4 June 1999, *Science*, Science's Compass, pp. 1622-23): Csermely argues that little attention is being paid to the fragmentation of the world's science literature. This is a major reason that it is so extremely difficult for individual scientists to have a broad-based appreciation for the "bigger picture". Csermely writes: **"There is only a limited effort to achieve the appropriate balance between the discovery of new facts and finding their proper place and importance in the framework of science."** This relates partly to what can be referred to as understanding the "significance", "impact", or "relevance" of one's work. Csermely goes on to note that **"science itself is not self-integrating, and there are fewer and fewer people taking responsibility for net-making". "Integration [of knowledge] needs time and patience..." "...greater credit should be given to those who make serious attempts to integrate their findings into the whole of human knowledge."**

Final Perspective

The Role of the Scientist

In Bruce Alberts' *2000 President's Address* to the National Academy of Sciences ("Science and Human Needs"), he addresses in part "the responsibilities of scientists" with the following words, which lend further, and final, perspective on the ideas presented in this discussion (available at: <http://www.nas.edu>).

"... (B)ecause political will is often short term, and misinformation about science abounds, **we scientists ourselves must become much more engaged in the everyday life of our governments and our communities.**" As 'civic scientists', "...in the 21st century, science and scientists will be judged on how well they help solve local and world problems, not only on how well they generate new knowledge. The impact of our research is everywhere, and we must step out and make sure that our work is understood and appropriately used by the world. ...We also need to be explicit about what is not known, and be clear about the questions that science cannot answer."

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is available at:**


**[http://www.epa.gov/esd/
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Environmental Aspects of Pharmaceuticals and Personal Care Products

EPA Grant Opportunities

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- [Critical Review Article](#) by Daughton and Ternes: **Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?**
-- [Summary/Background](#)
- [Media Coverage of EPA Activities in PPCPs](#)
- [ACS Symposium: Pharmaceuticals and Personal Care Products in the Environment: An Emerging Concern](#). A symposium organized for the 219th National Meeting of the American Chemical Society, San Francisco, CA, 27 March 200 [first all-day symposium in North America on this topic]:
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- [Listing of all Symposium Abstracts](#)
- [Daughton's Extended Abstract](#)
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